REMARKS

Claims 1, 26, 75, 84 and 85 have been amended. No new matter has been added. Claims 11 and 43 have been cancelled without prejudice. Applicants reserve the right to pursue the cancelled subject matter in a continuing application.

Applicants thank the Examiner for withdrawing the previous rejections of claim 83 under 35 U.S.C. § 102(b) and 35 U.S.C. § 102(e).

Claims 1-3, 5-10, 12-13, 26-33, 35-42, 44-45, 75-79, 81-82 and 84-89 are pending.

CLAIM REJECTIONS

Rejection of claims under 35 U.S.C. § 112, second paragraph

Claims 1-3 and 5-13

The Examiner has rejected claims 1-3 and 5-13 under 35 U.S.C. § 112, second paragraph, as being indefinite. See Office Action at p. 2. Claims 2-3 and 5-13 depend from independent claim 1. Specifically, the Examiner states that "[t]he term 'low' in claim 1 is a relative term which renders the claim indefinite." Id.

The Examiner contends that "the specification does not provide a limiting definition for a 'low' immunogenicity which would provide a boundary between that which is 'low' versus that which is not low, or 'moderate.'" Id. The Examiner further contends that "the immunogenic response to any given antigen is a function of the host as well as the antigen." Id. Applicants respectfully traverse this rejection.

MPEP 2173.05(b) states that

> [t]he fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph. *Seattle Box Co., v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification.
> ***
> When a term of degree is presented in a claim, first a determination is to be made as to whether the specification provides some standard for measuring that degree. If it does not, a determination is made as to whether one of ordinary skill in the art, in view of the prior art and the status of the art, would be nevertheless reasonably apprised of the scope of the invention. Even if the specification uses

the same term of degree as in the claim, a rejection may be proper if the scope of the term is not understood when read in light of the specification.

The phrase "low immunogenicity" is commonly used and well-understood by a person of skill in the art of antibody production. As previously explained, the phrase "low immunogenicity" is defined on p. 6, lines 30-32 of the specification, as "the inability of the natural molecule to elicit a strong immune response resulting in the production of high affinity antibodies." A person of ordinary skill in the art of antibody production would recognize or identify an antigen of low immunogenicity as an antigen that does not elicit a strong immune response to produce high affinity antibodies. A person of ordinary skill in the art of antibody production may use several characteristics of an antigen (described on p. 12, line 6 to page 13, line 6) to determine that an antigen has low immunogenicity, such as, for example, low-molecular weight compounds which are not capable of independently eliciting an immune response because of their small size, conservative low-immunogenic proteins, minor antigenic determinant that already has a very low percentage of all specific antibodies directed to it during the immune response, antigens with very high degree of conservation and are incapable of eliciting any noticeable immune response. Specific examples of such antigens are provided in Table 1.

Applicants submit that one skilled in the art of antibody production is able to ascertain what an "antigen of low immunogenicity" is in light of the claim in its entirety and the disclosure within the specification. Thus Applicants believe the phrase "low" as it applies to immunogenicity is not indefinite. Applicants thus respectfully request reconsideration and the withdrawal of this rejection.

Claim 80

The Examiner has rejected claim 80 under 35 U.S.C. § 112, second paragraph, as being indefinite. See Office Action at p. 3. Specifically, the Examiner contends that "[i]t is unclear how claim 80 further limits the scope of claim 75 ...." Id. Claim 80 has been cancelled thus rendering this rejection moot with respect to the claim.

Rejection of claims under 35 U.S.C. § 112, first paragraph

Enablement

The Examiner has rejected claims 1-3, 5-13, 26-33 and 35-45 under 35 U.S.C. § 112, first paragraph for lack of enablement. See Office Action at p. 3.

Specifically, the Examiner contends that "the specification, while being enabling for the method of claims 1, 14, 26, 74, 75, 84 and 85, wherein the hybridoma is produced by a fusion with a non-human immortalized mammalian cell, does not reasonably provide enablement for the methods of claims 1, 14, 26, 74, 75, 84 and 85, wherein fusion to provide the hybridoma is with a human immortalized cell, or wherein the screening for specificity is based on a 'protein A' assay." See Office Action at p. 3.

Claims 11 and 43

With respect to claims 11 and 43, the Examiner contends that "[t]he art teaches that chimeric hybridomas made by fusions of human B cells with mouse immortal cells are rare and that most such hybrids, with rare exceptions, tend to be highly unstable due to loss of human chromosomes ...." See Office Action at p. 4. The Examiner further maintains that "[i]t is reasonable to conclude that not all combinations of activated B cell and immortalized cell will produce a stable chimeric hybridoma secreting antibody" and that "[t]he specification fails to address this unreliability in the art." Id. As such, the Examiner contends that "one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to carry out the claimed methods using an immortalized human cell as the fusion partner for an animal B cell." Id. Applicants respectfully traverse this rejection. In an effort to expedite prosecution and not in acquiescence to the rejection, claims 11 and 43 have been cancelled without prejudice thus rendering this rejection moot with respect to those claims.

Claims 13 and 45

With respect to claims 13 and 45, the Examiner contends that "[o]ne of skill in the art would be subject to undue experimentation i[n] order to screen the secreted antibodies from the hybridomas using a protein A assay for IgG." See Office Action at p. 5. Applicants respectfully traverse this rejection. Applicants maintain that one of skill in the art of antibody production would consider utilizing protein A in a number of assays to screen for specificity of a monoclonal antibody to an antigen which would not require undue experimentation. However,

in an effort to expedite prosecution and not in acquiescence to the rejection, Applicants have deleted the phrase "protein A assay" from claims 13 and 45 without prejudice. Applicants understand that this specific rejection of claims 13 and 45 has been withdrawn based on the Examiner's comments in the Advisory Action.

Since the Examiner's rejection only specifically points to claims 13 and 45 and claims 11 and 43, Applicants believe that the remaining claims are enabled and respectfully request the withdrawal of this rejection.

Rejection of claims under 35 U.S.C. § 103

Cashman and Lussow

The Examiner has rejected claims 1-3, 8-10 and 13 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 7,041,807 to Cashman et al. ("Cashman") in view of Lussow et al., *European Journal of Immunology*, Vol. 21, pp. 2297-2302 (1991) ("Lussow"). See Office Action at p. 8. Claims 2-3, 8-10 and 13 depend from independent claim 1.

The Examiner contends that "Cashman et al teach a method comprising immunizing mice with prior proteins conjugated to KLH ..." and that "Luss[]ow et al teach that HSP 70 can substitute for a carrier molecule and induce a strong B cell response without the need for adjuvants as required for other carrier molecules ...." Id. The Examiner thus concludes that "[i]t would have been prima facie obvious to substitute HSP70 for the carrier protein used by Cashman et al" and that "[o]ne of skill in the art would have been motivated to do so by the teachings of Luss[]ow et al on the ability of HSP70 to provide a carrier effect and the induction of a strong antibody response." Id. Applicants respectfully traverse this rejection.

Amended claim 1 relates to a method of producing monoclonal antibodies specific to an antigen of low immunogenicity including a) conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein, b) immunizing a mammal with the conjugated antigen, the mammal having not been primed with BCG (Bacillus Calmette-Guerin); c) harvesting B cells from the mammal, d) creating hybridomas from the harvested B cells, e) screening the hybridomas for specificity to the native antigen.

Cashman describes "antibodies specific for PrP^{Sc} and diagnostic, therapeutic, and decontamination uses thereof." See Abstract. Cashman further describes that "monoclonal

antibodies against the same PrP^{Sc} -specific epitope were also generated, but with a derivative of the original antigen in which multiples of the original YYR peptide were linked together into one contiguous sequence." See col. 13, lines 6-10. Cashman also describes linking the YYRYYRYY peptide to KLH and that mice were immunized with the antigen. See col. 13, lines 15-17. Cashman does not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity including conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1.

This defect is not remedied by Lussow. Lussow describes the use of mycobacterial heat-shock proteins as carrier molecules in mice previously primed with live BCG. See p. 2300. Lussow further describes that "it was surprising (a) that priming with live BCG was required, and (b) that this in turn, eliminated the need for the use of adjuvants that are normally required when other carrier molecules are utilized." See p. 2301. Lussow is concerned with immunization and development of vaccine strategies. See p. 2301. Lussow emphasizes that "[i]n all cases, the antibody production took place with the hsp-peptide conjugate given in the *absence* of adjuvants, and required a previous priming with *live* BCG." (emphasis added). See p. 2300. Lussow presents data in Figure 1 and states that ""[a]n anti-peptide antibody response was never detectable in the two groups of mice receiving killed BCG." See p. 2299. Lussow does not teach or suggest does not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity including conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. In fact, a person of skill in the art would not be motivated to modify the teachings of Lussow and omit the priming of mice with *live* BCG to arrive at the method of claim 1. To avoid further confusion, Applicants have amended claim 1 to clarify that the mammal has not been primed with BCG (Bacillus Calmette-Guerin).

Further to Applicants' remarks concerning the Lussow reference, Applicants provide a Declaration of Petr Sveshnikov under 37 CFR 1.132 ("the Sveshnikov Declaration," attached at Appendix A), stating that:

> The Lussow reference is devoted to the study of the immunogenicity of a peptide antigen, namely the $(NANP)_{40}$ peptide. See paragraph 2.2 on p. 2298 of Lussow. This peptide was chemically conjugated with Py1 peptide, PPD, Hsp65, Hsp70 or ml18 using glutaraldehyde. See paragraph 2.2 on p. 2298 of Lussow. The main

goal of the authors was to demonstrate that a strong antibody response to the $(NANP)_{40}$ peptide antigen can be generated in mice by means of adjuvant-free immunization with the above-mentioned conjugates. In this regard, the data in Lussow demonstrated that priming with *live* BCG was necessary to induce an anti-peptide antibody response in the absence of adjuvants in mice that were genetically nonresponders to (NANP) peptides. See paragraph 3.1 on p. 2298-9 of Lussow. Lussow further discovered an anti-peptide antibody response was never detectable in two groups of mice receiving killed BCG. See paragraph 3.1 on p. 2298-9 of Lussow.

Lussow's discovery is significant for the development of adjuvant-free vaccines. As described in Lussow, "antibody production took place with the hsp-peptide conjugate given in the absence of adjuvants, and required a previous priming with live BCG." See Discussion at p. 2300 of Lussow. There is no mention in Lussow of producing monoclonal antibodies. Priming with live BCG (not heat-inactivated or lysates of BCG) is an integral requirement of all immunization schemes described in Lussow. In particular, paragraph 3.4 on p. 2299-2300 of Lussow which the Examiner points to on p. 8 of the Office Action, describes experiments conducted in mice previously primed with live BCG. See also figure legend of Figure 5. As such, a person of skill in the art who is reading Lussow would not be motivated to omit the priming of mice using live BCG from immunization of an animal since priming with live BCG is critical to Lussow's immunization schemes.

See paragraphs 3-4 of the Sveshnikov Declaration.

As such, the references, alone or in combination do not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity including conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1.

Accordingly, claim 1 and dependent claims thereof, are patentable over the combination of Cashman and Lussow for at least the reasons described above. Applicants respectfully request reconsideration and the withdrawal of this rejection.

Cashman, Lussow and Raven

The Examiner has rejected claims 1-3, 8-10, 13, 75 and 80-83 under 35 U.S.C. § 103(a) as being unpatentable over Cashman, Lussow and further in view of Raven. See Office Action at p. 8. Not in acquiescence to the rejection but in an effort to expedite prosecution, claims 80 and 83 have been cancelled thus rendering this rejection moot. Applicants respectfully request the

withdrawal of this rejection. Claims 2-3, 8-10 and 13 depend from independent claim 1. Claims 81 and 82 depend from independent claim 75.

As previously explained, Cashman and Lussow do not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity including conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. Cashman and Lussow do not teach or suggest a method of producing monoclonal antibodies specific to a Prion protein peptide including conjugating the Prion protein peptide chemically to a carrier molecule wherein the carrier molecule is HSP70 and wherein the prion protein peptide includes SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 9 as described in claim 75. To avoid further confusion, Applicants have amended claims 1 and 75 to clarify that the mammal has not been primed with BCG (Bacillus Calmette-Guerin).

This defect is not remedied by Raven. Raven describes immunizing VM mice that had previous been "inoculated with BCG to prime the immune response to inoculated peptide conjugates." See p. 12, lines 10-13. Raven further describes that "[f]or generation of monoclonal antibody cell lines, the spleen of the immunized mouse is removed and fused with myeloma cell lines using standard methods ...." See p. 17, lines 11-16. Raven does not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity including conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. Raven does not teach or suggest a method of producing monoclonal antibodies specific to a Prion protein peptide including conjugating the Prion protein peptide chemically to a carrier molecule wherein the carrier molecule is HSP70 and wherein the prion protein peptide includes SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 9 as described in claim 75. Indeed, based on the teachings of Lussow and Raven, a person of skill in the art would not be motivated to modify the teachings of Lussow and Raven to omit the priming of mice with BCG.

Accordingly, claims 1 and 75 and dependent claims thereof, are patentable over the combination of Cashman, Lussow and Raven for at least the reasons described above. Applicants respectfully request reconsideration and the withdrawal of this rejection.

Cashman, Lussow, Raven and Lawrence

The Examiner has rejected claims 1-3, 8-10, 13, 75, 76 and 80-83 under 35 U.S.C. § 103(a) as being unpatentable over Cashman, Lussow, Raven and further in view of U.S. Patent No. 4,859,613 to Lawrence ("Lawrence"). See Office Action at p. 9. Not in acquiescence to the rejection but in an effort to expedite prosecution, claims 80 and 83 have been cancelled thus rendering this rejection moot. Claims 2-3, 8-10 and 13 depend from independent claim 1. Claims 76, 81 and 82 depend from independent claim 75.

As previously explained, Cashman, Lussow, Raven do not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity including conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. Cashman, Lussow, Raven further do not teach or suggest a method of producing monoclonal antibodies specific to a Prion protein peptide including conjugating the Prion protein peptide chemically to a carrier molecule wherein the carrier molecule is HSP70 and wherein the prion protein peptide includes SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 9 as described in claim 75.

These defects are not remedied in Lawrence. Lawrence describes "[m]onoclonal antibodies specifically immunologically reactive to thiol-modified glutathione and hybridoma cell lines producing such monoclonal antibodies." See Abstract. Lawrence also describes "[a] method of producing antibodies specifically immunologically reactive with reduced glutathione by immunizing an animal using a thiol-modified glutathione, for example, a glutathione-N-ethylmaleimide-keyhole limpet hemocyanin conjugate." See Abstract. Lawrence does not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity including conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. Lawrence also does not teach or suggest a method of producing monoclonal antibodies specific to a Prion protein peptide including conjugating the Prion protein peptide chemically to a carrier molecule wherein the carrier molecule is HSP70 and wherein the prion protein peptide includes SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 9 as described in claim 75.

Accordingly, claims 1 and 75 and dependent claims thereof, are patentable over the combination of Cashman, Lussow, Raven and Lawrence for at least the reasons described above. Applicants respectfully request reconsideration and the withdrawal of this rejection.

Seiki and Lussow

The Examiner has rejected claims 1-3, 6, 8-10, 13, 85 and 87-89 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,191,255 to Seiki et al. ("Seiki") in view of Lussow. See Office Action at p. 10. Claims 2-3, 6, 8-10 and 13 depend from independent claim 1. Claims 87-89 depend from independent claim 85.

The Examiner contends that "[i]t would have been prima facie obvious to substitute HSP70 for the carrier protein used by Seiki et al." Id. The Examiner further contends that "[o]ne of skill in the art would have been motivated to do so by the teachings of Luss[]ow et al on the ability of HSP70 to provide a carrier effect and the induction of a strong antibody response." Id. Applicants respectfully traverse this rejection.

Seiki describes methods of making a monoclonal antibody to human MT-MMP-3 and further describes that fragment so MT-MMP-3 "be coupled with various carrier proteins via suitable coupling agents to form immunogenic conjugates such as hapten-proteins." See col. 18, lines 27-36 and col. 18, line 63 to col. 19, line 3. Seiki further states that "[t]he carrier proteins include keyhole limpet haemocyanin (KLH), bovine serum albumin (BSA), ovalbumin, globulin, polypeptides such as polylysine, bacterial components such as BCG or the like." See col. 19, lines 15-18. Seiki does not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity including conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. Seiki additionally does not teach or suggest a method of producing monoclonal antibodies specific to matrix metalloprotease 3 including conjugating the matrix metalloprotease 3 chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein as described in claim 85.

This defect is not remedied by Lussow contrary to the Examiner's assertion. As previously explained, Lussow describes the use of mycobacterial heat-shock proteins as carrier molecules in mice previously primed with live BCG. See p. 2300. Lussow emphasizes that "[i]n

all cases, the antibody production took place with the hsp-peptide conjugate given in the *absence* of adjuvants, and required a previous priming with *live* BCG." (emphasis added). See p. 2300. Lussow presents data in Figure 1 and states that ""[a]n anti-peptide antibody response was never detectable in the two groups of mice receiving killed BCG." See p. 2299. Contrary to the Examiner's assertion, a person of skill in the art would not be motivated to modify the teachings of Lussow and omit the priming of mice with *live* BCG to arrive at the method of claim 1 or claim 85. To avoid further confusion, Applicants have amended claims 1 and 85 to clarify that the mammal has not been primed with BCG (Bacillus Calmette-Guerin).

Accordingly, Lussow does not teach or suggest does not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity including conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1 or 85. Seiki additionally does not teach or suggest a method of producing monoclonal antibodies specific to matrix metalloprotease 3 including conjugating the matrix metalloprotease 3 chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein as described in claim 85.

Accordingly, claims 1 and 85 and dependent claims thereof, are patentable over the combination of Seiki and Lussow for at least the reasons described above. Applicants respectfully request reconsideration and the withdrawal of this rejection.

Seiki, Lussow and Lawrence

The Examiner has rejected claims 1-3, 6, 8-10, 13, 85 and 87-89 under 35 U.S.C. § 103(a) as being unpatentable over Seiki and Lussow and further in view of Lawrence. See Office Action at p. 10. Claims 2-3, 6, 8-10 and 13 depend from independent claim 1. Claims 87-89 depend from independent claim 85.

As explained above, Seiki and Lussow do not teach or suggest does not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity including conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. Seiki and Lussow additionally do not teach or suggest a method of producing monoclonal antibodies specific to matrix metalloprotease 3

including conjugating the matrix metalloprotease 3 chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein as described in claim 85.

These defects are not remedied by Lawrence either. Lawrence describes "[m]onoclonal antibodies specifically immunologically reactive to thiol-modified glutathione and hybridoma cell lines producing such monoclonal antibodies." See Abstract. Lawrence also describes "[a] method of producing antibodies specifically immunologically reactive with reduced glutathione by immunizing an animal using a thiol-modified glutathione, for example, a glutathione-N-ethylmaleimide-keyhole limpet hemocyanin conjugate." See Abstract. Lawrence does not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity including conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. Lawrence also does not teach or suggest a method of producing monoclonal antibodies specific to matrix metalloprotease 3 including conjugating the matrix metalloprotease 3 chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein as described in claim 85.

Accordingly, claims 1 and 85 and dependent claims thereof, are patentable over the combination of Seiki, Lussow and Lawrence for at least the reasons described above. Applicants respectfully request reconsideration and the withdrawal of this rejection.

Filit, Berzofsky, Lussow and Yokoyama

The Examiner has rejected claim 84 under 35 U.S.C. § 103(a) as being unpatentable over Filit et al., *Journal of Experimental Medicine*, Vol. 164, p. 762-776 (1986) ("Filit") in view of Berzofsky et al., *"Antigen-Antibody Interactions and Monoclonal Antibodies," In: Fundamental Immunology,* W.E. Paul, Ed. P. 458 (1993) ("Berzofsky"), Lussow and Yokoyama, *"Production of Monoclonal Antibodies," In: Current Protocols in Immunology*, Unit 2.5 (1991) ("Yokoyama"). See Office Action at p. 11.

Claim 84 relates to a method of producing monoclonal antibodies specific to hyaluronic acid including a) conjugating the hyaluronic acid chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein, b) immunizing a mammal with the conjugated antigen, the mammal having not been primed with BCG (Bacillus Calmette-Guerin), c) harvesting B cells

from the mammal, d) creating a hybridoma from the harvested B cells and e) screening the hybridomas for specificity to the native hyaluronic acid.

Fillit describes "induction of antibodies to hyaluronic acid by immunization of rabbits with encapsulated streptococci." See Title and Abstract. Fillit does not teach or suggest a method of producing monoclonal antibodies specific to hyaluronic acid that includes conjugating the hyaluronic acid chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein.

This defect is not remedied by Berzofsky, Yokoyama or Lussow. Berzofsky describes the general applications of monoclonal antibodies. See p. 458. Yokoyama describes protocols for production of monoclonal antibodies. Both Berzofsky and Yokoyama do not teach or suggest a method of producing monoclonal antibodies specific to hyaluronic acid that includes conjugating the hyaluronic acid chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein. Further, as previously explained, Lussow describes the use of mycobacterial heat-shock proteins as carrier molecules in mice previously primed with live BCG. See p. 2300. Lussow further describes that "it was surprising (a) that priming with live BCG was required, and (b) that this in turn, eliminated the need for the use of adjuvants that are normally required when other carrier molecules are utilized." See p. 2301. Lussow does not teach or suggest a method of producing monoclonal antibodies specific to hyaluronic acid that includes conjugating the hyaluronic acid chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein. There is no motivation or suggestion in Lussow or any of the references to modify the teachings of Lussow. As previously explained, a person of skill in the art would not be motivated to modify the teachings of Lussow and omit the priming of mice with *live* BCG to arrive at the method of claim 84. To avoid further confusion, Applicants have amended claim 84 to clarify that the mammal has not been primed with BCG (Bacillus Calmette-Guerin).

Accordingly, claim 84 is patentable over the combination of Fillit, Berzofsky, Lussow and Yokoyama. Applicants respectfully request reconsideration and the withdrawal of this rejection.

Zatsepina, Yokoyama, Lussow and Wu

The Examiner has rejected claims 1-3, 5, 8-10, 13, 26, 27, 32, 33, 35, 36, 39-42 and 45 under 35 U.S.C. § 103(a) as being unpatentable over Zatsepina et al., *Oncogene*, Vol. 14, pp. 1137-1145 (1997) ("Zatsepina"), Yokoyama, Lussow and U.S. Publication No. 2004/0086845 to Wu et al. ("Wu"). See Office Action at p. 12. Claims 2-3, 5, 8-10 and 13 depend from independent claim 1. Claims 27, 32-33, 35-36, 39-42 and 45 depend from independent claim 26.

The Examiner contends that "[i]t would have been prima facie obvious to immunize the mice with E7 fused to HSP70." See Office Action at p. 13. The Examiner further contends that "[o]ne of skill in the art would be motivated to do so by the teachings of Wu et al on the low immunogenicity of the E7 protein and the teachings of Lussow et al on the strong induction of antibodies using HSP70 as a carrier for antigen." Id. Applicants respectfully traverse this rejection.

Zatsepina describes the generation of HPV16 E7 monoclonal antibodies. See p. 1138. Zatsepina does not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity that includes conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein. Zatsepina further does not teach or suggest a method of producing monoclonal antibodies specific to E7 oncoprotein including conjugating the E7 oncoprotein chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein.

These defects are not remedied by the other references. Yokoyama describes protocols for production of monoclonal antibodies. However, Yokoyama does not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity including conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. Yokoyama further does not teach or suggest a method of producing monoclonal antibodies specific to E7 oncoprotein including conjugating the E7 oncoprotein chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein. Wu describes "[n]ucleic acids encoding a chimeric or fusion polypeptide which polypeptide comprises a first domain comprising a translocation polypeptide; and a second domain comprising at least one antigenic peptide ...." See Abstract. Wu does not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity that includes conjugating the antigen chemically to a carrier molecule, wherein

the carrier molecule is a heat-shock protein. Wu further does not teach or suggest a method of producing monoclonal antibodies specific to E7 oncoprotein including conjugating the E7 oncoprotein chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein.

Further, as previously explained, Lussow does not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity that includes conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein. Lussow further does not teach or suggest a method of producing monoclonal antibodies specific to E7 oncoprotein including conjugating the E7 oncoprotein chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein. There is no motivation or suggestion in Lussow or any of the references to modify the teachings of Lussow. For reasons previously explained, a person of skill in the art would not be motivated to modify the teachings of Lussow and omit the priming of mice with *live* BCG to arrive at the method of claim 1 or claim 26. To avoid further confusion, Applicants have amended claims 1 and 26 to clarify that the mammal has not been primed with BCG (Bacillus Calmette-Guerin).

Accordingly, claims 1, 26 and dependent claims thereof are patentable over the combination of Zatsepina, Yokoyama, Lussow and Wu. Applicants respectfully request reconsideration and the withdrawal of this rejection.

Zatsepina, Lussow, Wu, Yokoyama and Seiki

The Examiner has rejected claims 1-3, 5, 6, 8-10, 13, 26, 27, 32-33, 36, 37, 39-42 and 45 under 35 U.S.C. § 103(a) as being unpatentable over Zatsepina, Lussow, Wu and Yokoyama and further in view of Seiki. See Office Action at p. 13. Claims 2-3, 5, 6, 8-10 and 13 depend from independent claim 1. Claims 27, 32-33, 36, 37, 39-42 and 45 depend from independent claim 26.

As previously explained, Zatsepina, Lussow, Wu and Yokoyama, alone or in combination, do not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity that includes conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. Zatsepina, Lussow, Wu and Yokoyama, alone or in combination, also do not teach or suggest a method of producing monoclonal antibodies specific to E7 oncoprotein including conjugating the

E7 oncoprotein chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein as described in claim 26.

Seiki describes methods of making a monoclonal antibody to human MT-MMP-3 and further describes that fragment so MT-MMP-3 "be coupled with various carrier proteins via suitable coupling agents to form immunogenic conjugates such as hapten-proteins." See col. 18, lines 27-36 and col. 18, line 63 to col. 19, line 3. Seiki further states that "[t]he carrier proteins include keyhole limpet haemocyanin (KLH), bovine serum albumin (BSA), ovalbumin, globulin, polypeptides such as polylysine, bacterial components such as BCG or the like." See col. 19, lines 15-18. Seiki does not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity that includes conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. Seiki further does not teach or suggest a method of producing monoclonal antibodies specific to E7 oncoprotein including conjugating the E7 oncoprotein chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein as described in claim 26.

Accordingly, claims 1, 26 and dependent claims thereof are patentable over the combination of Zatsepina, Lussow, Yokoyama, Wu and Seiki. Applicants respectfully request reconsideration and the withdrawal of this rejection.

Zatsepina, Lussow, Wu, Yokoyama and Burnett

The Examiner has rejected claims 1-3, 5, 8-10, 13, 26, 27, 32, 33, 35-36, 39-42 and 45 under 35 U.S.C. § 103(a) as being unpatentable over Zatsepina, Lussow, Wu and Yokoyama and further in view of Burnett. See Office Action at p. 13. Claims 2-3, 5, 8-10 and 13 depend from independent claim 1. Claims 27, 32-33, 35-36, 39-42 and 45 depend from independent claim 26.

As previously explained, Zatsepina, Lussow, Wu and Yokoyama, alone or in combination, do not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity that includes conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. Zatsepina, Lussow, Wu and Yokoyama, alone or in combination, also do not teach or suggest a method of producing monoclonal antibodies specific to E7 oncoprotein including conjugating the

E7 oncoprotein chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein as described in claim 26.

These defects are not remedied in Burnett. Burnett on p. 115 (as cited by the Examiner) describes "peripheral blood as a source of antigen-primed lymphocytes." Burnett does not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity including conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. Burnett further does not teach or suggest a method of producing monoclonal antibodies specific to E7 oncoprotein including conjugating the E7 oncoprotein chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein as described in claim 26.

Accordingly, claims 1, 26 and dependent claims thereof are patentable over the combination of Zatsepina, Lussow, Yokoyama, Wu and Burnett. Applicants respectfully request reconsideration and the withdrawal of this rejection.

Zatsepina, Lussow, Wu, Yokoyama and Zwerschke

The Examiner has rejected claims 1-3, 5, 8-10, 13, 26, 27, 31-33, 35, 36, 39-42 and 45 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Zatsepina, Lussow, Wu and Yokoyama and further in view of WO 2003/080669 to Zwerschke ("Zwerschke"). See Office Action at p. 14. Claims 2-3, 5, 8-10 and 13 depend from independent claim 1. Claims 27, 31-33, 35-36, 39-42 and 45 depend from independent claim 26.

As previously explained, Zatsepina, Lussow, Wu and Yokoyama, alone or in combination, do not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity that includes conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. Zatsepina, Lussow, Wu and Yokoyama, alone or in combination, also do not teach or suggest a method of producing monoclonal antibodies specific to E7 oncoprotein including conjugating the E7 oncoprotein chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein as described in claim 26.

These defects are not remedied in Zwerschke. Zwerschke describes "an anti-HPV-16 E7 antibody obtainable by (a) eliciting an in vivo humoral response against highly purified HPV-16

E7 protein or a fragment thereof in a non-human vertebrate ...." See Abstract. Zwerschke does not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity that includes conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. Zwerschke also does not teach or suggest a method of producing monoclonal antibodies specific to E7 oncoprotein including conjugating the E7 oncoprotein chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein as described in claim 26.

Accordingly, claims 1, 26 and dependent claims thereof are patentable over the combination of Zatsepina, Lussow, Yokoyama, Wu and Zwerschke. Applicants respectfully request reconsideration and the withdrawal of this rejection.

Zatsepina, Lussow, Wu, Yokoyama and Milstein

The Examiner has rejected claims 1-3, 5, 8-10, 12-13, 26-27, 32-33, 35, 39-42 and 45 under 35 U.S.C. § 103(a) as being unpatentable over Zatsepina, Lussow, Wu and Yokoyama and further in view of Milstein, "Monoclonal Antibodies from Hybrid Myelomas," *In: Monoclonal Antibodies in Clinical Medicine,* McMichael and Favre, Eds, p. 9 (1982) ("Milstein"). See Office Action at p. 14. Claims 2-3, 5, 8-10 and 12-13 depend from independent claim 1. Claims 27, 32-33, 35-36, 39-42 and 44-45 depend from independent claim 26.

As previously explained, Zatsepina, Lussow, Wu and Yokoyama, alone or in combination, do not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity that includes conjugating the antigen chemically to a carrier molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. Zatsepina, Lussow, Wu and Yokoyama, alone or in combination, also do not teach or suggest a method of producing monoclonal antibodies specific to E7 oncoprotein including conjugating the E7 oncoprotein chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein as described in claim 26.

These defects are not remedied by Milstein. Milstein describes "that hybridomas can be made by fusing rat or mouse spleen cells with rat myeloma cells." See Office Action at p. 15. Milstein does not teach or suggest a method of producing monoclonal antibodies specific to an antigen of low immunogenicity including conjugating the antigen chemically to a carrier

molecule, wherein the carrier molecule is a heat-shock protein as described in claim 1. Milstein also does not teach or suggest a method of producing monoclonal antibodies specific to E7 oncoprotein including conjugating the E7 oncoprotein chemically to a carrier molecule wherein the carrier molecule is a heat-shock protein as described in claim 26.

Accordingly, claims 1, 26 and dependent claims thereof are patentable over the combination of Zatsepina, Lussow, Yokoyama, Wu and Milstein. Applicants respectfully request reconsideration and the withdrawal of this rejection.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims now pending are in condition for allowance. A petition for an extension of time is attached.

Should any fees be required by the present Amendment, the Commissioner is hereby authorized to charge Deposit Account **19-4293**.

Respectfully submitted,

Date: 4-22-10

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